REMARKS/ARGUMENTS

Reconsideration and continued examination of the above-identified application are respectfully requested.

The amendment to the claims further defines what the applicants regard as their invention. In particular, claims 1-3, 11-14, and 19-24 have been amended as explained below. Claims 7-10 and 15-18 have been canceled. Full support for this amendment can be found throughout the present application, for example, on pages 18, 19, 22, and 23. Accordingly, no questions of new matter should arise and entry of this amendment is respectfully requested.

Objection of Claims 1-14, 20, and 23

At page 3 of the Office Action, the Examiner objected to claims 1-14, 20, and 23 for the improper use of numbers within the claims. In particular, the Examiner stated that in claims 1, 7, 11, 13, 20, and 23, itemized sequence steps use integers (i.e., 1, 2, etc.), but these integers are usually reserved for claims. The Examiner suggested that the sequence steps be distinguished by using other sequential characters such as a, b, c, or i, ii, iii, etc. For the following reasons, this objection is respectfully traversed.

Claims 1, 11, 13, 20, and 23 have been amended by replacing the integers with letters that are used to itemize the sequence steps as suggested by the Examiner. Claims 7-10 have been cancelled as indicated above.

Therefore, this objection should be withdrawn.

Objection of Claims 7, 9, and 10

At page 3 of the Office Action, the Examiner objected to claims 7, 9, and 10 as being of

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improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that claim 7 requires the contacting of a compound with a three-dimensional structure, establishing/evaluating an interaction and detecting a signal of the interaction, which is not a narrower limitation of claim 1 (step 5), that requires the screening of a compound. The Examiner alleged that claim 1 requires the examination or testing of a group of compounds to separate those who interact from those who have a defective characteristic preventing interaction, wherein discrimination of compounds necessitates detecting a signature signal for interaction. The Examiner further alleged that claims 9 and 10 are not narrower limitations of claims 1 and 7, respectively, as the limitations of both claims 9 and 10 have been already established in claim 1, step 2. At page 4 of the Office Action, the Examiner further stated that if claims 1 and 2 are found to be allowable, claims 7-10 would be objected to as being a substantial duplicate thereof. The Examiner also objected to claims 7, 9, and 10 for informalities, as listed on page 4 of the Office Action. For the following reasons, this objection is respectfully traversed.

Claims 7-10 have been canceled and therefore this objection is now moot.

Rejection of Claims 1-14 and 19-24 Under 35 U.S.C. §112, Second Paragraph

At page 5 of the Office Action, the Examiner rejected claims 1-14 and 19-24 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner cited Rigas (GASTROENTEROLOGY, Vol. 111, 1996, pp. 523-526). In particular, the Examiner stated that in claims 1, 11, 13, 19, 20, 21, and 23 (note: the Examiner's listing of claim 21 is in error here), the term "variation" is indefinite because the specification does not define how "variation" is to be determined. The Examiner alleged that because there are so many alleles as demonstrated by

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Rigas, the determination of variation based upon analysis of a single or multiple alleles is questionable. For the following reasons, this rejection is respectfully traversed.

Applicants have amended the method claims in order to recite "variations of at least one amino acid of the at least one position of the at least one polymorphic amino acid" and further defined "variation" in a similar fashion for the product claims. The claims are now clear that the "variation" is of at least one amino acid of the at least one position of the at least one polymorphic amino acid. Therefore, the variations pertain to analysis of at least one amino acid of one or more alleles selected from at least one amino acid sequence encoded by at least one of DRB1* gene, DQB1* gene, and the DPB1* gene of HLA, as recited in independent claim 1, subparagraph a, in independent claim 11, subparagraph a, in independent claim 13, subparagraph a, in independent claim 19 and in independent claim 22. Therefore, this rejection should be withdrawn.

At page 5 of the Office Action, the Examiner alleged that claims 1-10 failed to accomplish the preamble of "determine effective cancer treatment" which is done *in silico* as required by step 5 of claim 1. The Examiner further stated that claims 4-6 cannot be accomplished *in silico* and that claim 7 is also done *in silico* and fails to accomplish the preamble of the independent claim. For the following reasons, this rejection is respectfully traversed.

First, the claims use "comprising" language and not "consisting" language. Therefore, it is improper to state that claims 1-10 fail to accomplish the preamble of "determine effective cancer treatment" by referring only to step 5 of claim 1, which can be performed *in silico*. However, claim 1 has been amended by inserting additional steps (f) and (g) which clearly allows determination of an effective cancer treatment.

Therefore, this rejection should be withdrawn.

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At page 6 of the Office Action, the Examiner rejected claims 2, 8, 12, 14, 21, and 24 because the Examiner alleged that these claims recite the phrase "wherein cancer is analyzed by distinguishing stomach cancer from other cancers," but the corresponding independent claims do not provide any method steps for how such an analysis for distinguishing cancer types is accomplished. For the following reasons, this rejection is respectfully traversed.

Claim 1 has been amended by inserting steps (f) and (g) in order to recite the step of correlating the candidate compounds for cancer treatment medicine with a reduction or lack of growth of cancer cells and/or tumors or a reduction of the rate of cancer metastases (see pages 22-23 of the present application) and providing statistical significant relationships by combining and evaluating information from the previous steps. Claims 2, 12, 14, 21, and 24, have been amended to recite that the statistically significant relationship is analyzed. Claim 8 has been canceled. Therefore, this rejection should be withdrawn.

At page 6 of the Office Action, the Examiner rejected claim 3 as being indefinite in the recitation of the "three-dimensional structure of the candidate compounds" since it lacks antecedent basis. For the following reasons, this rejection is respectfully traversed.

Claim 3 has been amended by reciting "a three-dimensional structure." Therefore, this rejection should be withdrawn.

Also, at page 6 of the Office Action, the Examiner rejected claim 7, based on the recitation of the phrase "variation of each amino acid" in step 1. At page 7 of the Office Action, the Examiner rejected claim 7, because step 2 recites the phrase "detecting a signal of the interaction," which the Examiner considers to be unclear. This rejection is now moot in view of the cancellation of claim 7.

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At pages 7-8 of the Office Action, the Examiner rejected claims 22-24 for several reasons regarding indefiniteness. In particular, the Examiner stated that the phrase "a polymorphic variation of a DRB1* gene, DQB1* gene, and DPB1* gene of HLA" is confusing, that "polypeptide encoding a polymorphic variation of..." is incorrect in claim 22, and that in claim 24, "the method according to claim 23" is incorrect because claim 23 is drawn to a composition. For the following reason, this rejection is respectfully traversed.

Claim 22 has been amended by reciting "an isolated polypeptide encoded by a polymorphic variation of a DRB1* gene, DBB1* gene, or DPB1* gene of HLA." Claim 24 has been amended to recite the "The composition according to claim 23." Therefore, this rejection should be withdrawn.

Rejection of Claims 1-14 and 19-24 Under 35 U.S.C. §112, First Paragraph - Written Description

At page 8 of the Office Action, the Examiner rejected claims 1-14 and 19-24 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner alleged that the specification lacks a clear and concise structural and functional correlation for the claimed genera. The Examiner cited Gorski et al. (J. IMMUNOLOGY, Vol. 143, 1989, pp. 329-333). The Examiner further alleged that although applicants seemed to establish that the HLA class II encoded polypeptides encompassed by the broad claims are full-length HLA class II polypeptides consisting of a heterodimer between an invariant α chain and a polymorphic β chain, there is no clear description, such as a SEQ ID identifier, number of amino acid residues, or nucleotides in the specification. Furthermore, the Examiner stated that multiple human variants of HLA class II exist in nature as demonstrated by Gorski et al., more could be

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generated in the lab, and the claims are not limited to specific polymorphic variants. Thus, the Examiner took the position that without identifying and sequencing each one, there is no way to know what their sequences are, and that the applicants have not disclosed, nor does the art recognize, the requisite structural and functional features of all the contemplated nucleic acid and amino acid sequence possibilities recited in the instant claims, which result in the disclosed statistical significant relationship with a cancer treatment, a feature deemed essential to the instant invention.

At page 12 of the Office Action, the Examiner further alleged that neither the specification nor the claims as written make such distinctions between two polymorphic domains involved in distinct functions, that there are no descriptions of variable regions in the polynucleotide or the encoded polypeptide that correlate with a statistical significant relationship with a cancer, that a person skilled in the art would not recognize which polymorphic domains are essential for practicing the claimed invention, and that it is unclear as to which regions of the polypeptide are useful to screen for cancer treatment medicines, which is a feature essential to generate suitable screening three-dimensional models representative of the encoded polypeptides. For the following reasons, this rejection is respectfully traversed.

The independent claims have been amended to recite the specific possible positions for variations in the HLA genes, specifically for the DQB1* gene, the DRB1* gene, and the DPB1* gene as listed on pages 18-23 of the description and now recited in independent claims 1, 11, 13, 19, and 22. Applicants submit that the polymorphic domains are now clear based on the specifically recited positions within the specifically recited genes.

Therefore, this rejection should be withdrawn.

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At pages 12-13 of the Office Action, the Examiner alleged that because the genus of polypeptides encoded by HLA genes, DRB1*, DQB1*, and DPB1* are not adequately described, it follows that a model derived from said genus of polypeptides encompasses a population of species widely variant in structure and atomic composition. The Examiner further alleged that the three-dimensional structure/models are limited to the polymorphic β chain and not the HLA class II heterodimer and, therefore, the applicants have failed to describe all possible crystal forms containing the claimed genera of polypeptides that are necessary to obtain structure coordinates. For the following reason, this rejection is respectfully traversed.

The comments above, with respect to the amendment of the independent claims, apply equally here. Therefore, this rejection should be withdrawn.

Rejection of Claims 1-10 Under 35 U.S.C. §112, First Paragraph - Enablement

At page 14 of the Office Action, the Examiner rejected claims 1-10 under 35 U.S.C. §112, first paragraph, scope of enablement, because the specification, while enabling for *in silico* screening of compounds using a homology model of an entire HLA heterodimer structure (or a defined binding pocket within said model), does not reasonably provide enablement for making new crystals from which a three-dimensional model could be generated or homology modeling of the β chain of an HLA heterodimer. For the following reasons, this rejection is respectfully traversed.

The arguments against the rejection of claim 1-10 above and the comments regarding the amendment above apply equally here. Additionally, claim 1 has been amended to recite "an evaluating method to determine effective cancer treatment medicines" instead of "a screening method" for the preamble of claim 1 and to recite the specific positions of the specific genes at

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issue in conjunction with the amino acids encoded by the genes.

Therefore, this rejection should be withdrawn.

Rejection of Claims 11-14 Under 35 U.S.C. § 103(a) over Davies et al. in view of Lee et al.

At page 23 of the Office Action, the Examiner rejected claims 11-14 under 35 U.S.C. §103(a) as being obvious over Davies et al. (J. CLINICAL ONCOLOGY, Vol. 19, March 2001, pp. 1279-1287) in view of Lee et al. (GASTROENTEROLOGY, Vol. 111, 1996, pp. 426-432). In particular, the Examiner alleged that Davies et al. teaches a method for evaluating cancer treatments based on genotyping polymorphic genes of patients receiving cancer therapy and correlating the survival results of patients containing a specific polymorphic gene with appropriate cancer treatment regimens (see Abstract, p. 1279). The Examiner further alleged that the reference teaches that the polypeptides encoded by polymorphic genes of Glutathione S-transferase, i.e., theta (GSTT1) and mu (GSTM1), affect the cytotoxicity of chemotherapeutic drugs. The Examiner, however, acknowledged that Davies et al. does not teach any association of HLA Glass II genes with any cancer. The Examiner, however, alleged that Lee et al. teaches that HLA Class II genes are associated with several cancers (see lines 1-2, first column, page 426). The Examiner concluded that one of ordinary skill in the art would be able to use the genotyping methods of Davies et al. or Lee et al., along with the statistical methods of Davies et al. to identify HLA Class II polymorphic genes of patients receiving anti-cancer therapy and correlating the survival results of HLA Class II genotype with appropriate cancer treatment regimens. For the following reasons, this rejection is respectfully traversed.

Claim 11 has been amended to recite the specific positions of the specific genes with respect to the specific polymorphic amino acids that are evaluated which neither Davies et al. nor

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Lee et al. teaches or suggests.

Therefore, this rejection should be withdrawn.

Rejection of Claims 1-10 Under 35 U.S.C. 103(a) over Davies et al. in view of Lee et al., Toh et al., and Gibbs et al.

At page 25 of the Office Action, the Examiner rejected claims 1-10 under 35 U.S.C. §103(a) as being obvious over Davies et al., in view of Lee et al., Toh et al. (PROTEIN ENGINEERING, Vol. 11, 1998, pp. 1027-1032) and Gibbs et al. (SCIENCE, Vol. 287, 2000, pp. 1969-1973). The Examiner alleged that the teachings of Davies et al. and Lee et al. are set forth previously, but acknowledged that these references do not teach a homology model of an HLA Class II polypeptide that would be used *in silico* screening of compounds. However, the Examiner alleged that Toh et al. teaches a homology model HLA Class II heterodimer, namely HLA-DRB1*0405 (see page 1027, second column, preparation of input coordinates). The Examiner concluded that it would have been obvious of one of ordinary skill in the art to evaluate a candidate therapy for cancer or associated it with a polymorphic gene comprising *in silico* screening of a compound with a homology model consisting of a specific polymorphic HLA Class II polypeptide because it was well known in the art that HLA Class II polymorphic genes, such as HLA-DQB1*0301 of Lee et al., were associated with several types of cancer, including adenocarcinomas of the stomach. The Examiner further alleged that Gibbs et al. also teaches the successful screening of compounds to molecular targets that has resulted in the identification of new therapies now being realized on a large scale in the clinic, and also acknowledged that Gibbs et al. is silent about *in silico* screening methods. The Examiner concluded that because simply changing the screening method to be used is not beyond the

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ordinary skill of the art, the references, taken together, reasonably suggest to one of ordinary skill in the art to use the homology model of Toh et al. to create a three-dimensional model of HLA Class II heterodimer, either to screen for compounds that interact with a polymorphic HLA Class II polypeptide that has been associated with cancer or to screen for additional compounds that interact with specific polymorphic HLA Class II polypeptides that have been correlated with a particular cancer treatment regimen. For the following reasons, this rejection is respectfully traversed.

Claim 1 has been amended to recite the specific positions of the specific genes with respect to the specific polymorphic amino acids that are evaluated which neither Davies et al. nor Lee et al. teaches or suggests. Toh et al. and Gibbs et al. do not cure the deficiencies of Davies et al. or Lee et al.

Therefore, this rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks, the applicant respectfully requests the reconsideration of this application and the timely allowance of the pending claims.

If there are any other fees due in connection with the filing of this Amendment, please charge the fees to Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such extension is requested and should also be charged to our Deposit Account.

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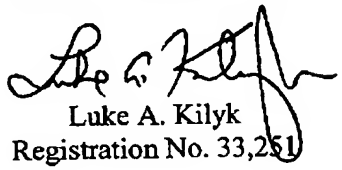
Response to Office Action dated February 24, 2006

Respectfully submitted,



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